

REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 1-9, 12-17, 19-33, 35-38 and 42-78 are in the case and are before the Examiner.

I. The Amendments

Each of independent claims 1, 18, 42, 63, 74, 75 and 78 has been amended to recite that the percentage of replacement residues is "as compared to a sequence of SEQ ID NO:246-251 from position 1 through 149". Support for these amendments can be found at least in the disclosure of the major paragraph at page 47

It is thus seen that no new matter has been added.

II. The Action

A. Rejections Under 35 USC §112,
Second Paragraph

The Action has asserted that the claims are "replete" with ambiguities and are other wise indefinite for several reasons. These bases for rejection are taken up below in the order of their appearance in the Action and are respectfully traversed.

(1) "conservatively substituted"

The specification is said to provide inconsistent definitions for the term "conservatively substituted" as used in claims 1, 18, 42, 63, 75 and 78. The Action has rejected the definition of that term found on page 18 as not being a limiting definition.

The Examiner's attention is invited on this point to the enclosed Exhibits 1 and 2 that contain definitions of "conservative substitution" from two published dictionaries pertinent to this field: the Oxford Dictionary of Biochemistry and Molecular Biology, and the Concise Dictionary of Biomedicine and Molecular Biology. As will be seen, those definitions are substantially the same definition that is found on page 18 of the specification.

Still further, Exhibit 3 is a list taken from the USPTO data base of presumptively valid US patents whose claims recite the phrase "conservatively substituted". Exhibit 4 are pages prepared by the undersigned showing the definitions for that phrase taken from the five most recently issued patents. It will be seen that the definitions contained therein differ among themselves when they are given, but it will be also seen that there is substantial agreement with the definition given on page 18 herein. Inasmuch as a patent is directed to those of ordinary skill in the art, it is submitted that a skilled worker would understand the definition used and would be on notice of the metes and bounds of the claims.

In reviewing the original basis for rejection, it is believed that the Action has misunderstood the disclosure at pages 47-48 in regard to the treatment of deletions. It is submitted that that disclosure simply teaches the reader how to treat a deletion in calculating the percentage of substitution as recited in the claims. That portion does not define a deletion as a conservative substitution, but rather teaches the skilled worker to treat a deletion as a conservative substitution only when calculating the percentage of substitution. As such, there is no ambiguity nor

indefiniteness, and this basis for rejection should be withdrawn.

(2) Sequence Comparison

The Action reiterated its rejection related to a HBc sequence with which to compare the percentage of substitution. It seemed clear that the specification taught at least in the paragraph bridging pages 22 and 23 that one could choose any HBc sequence, and that was so stated in the prior Reply. However, the present Action noted that even though several mammalian sequences are disclosed, none is specifically recited in the claims, and that a given percentage relative to one sequence could be different for another sequence. That understanding was correct in that HBc was being used as a generic expression for any mammalian sequence because any of the recited sequences could be used because they are so similar and have similar particle-forming properties as is recited in the cited paragraph bridging pages 22 and 23. Nonetheless, in an effort to speed prosecution, the present amendments recite that one can make the comparison to any of the recited HBc sequences of Fig. 7 from position 1 through 149 of those sequences.

It is thus submitted that this basis for rejection should also be withdrawn.

(3) "5 residues from HBc
position 135 to the HBc terminus"

(4) "Domain IV contains zero through
fourteen residues of a HBc ..."

(5) "heterologous linker residue..."

(6) "of at least about"
and "up to about"

(7) Claims 18 and 19

(8) Claims 63 and 66

(9) Claim 70

It is noted with appreciation that the above bases for rejection (3-9) under 35 USC §112, Second Paragraph have been withdrawn.

B. Rejection Under 35 USC §112, First Paragraph

All of the pending claims were rejected under 35 USC §112, First Paragraph, as allegedly lacking enablement. The Action placed its basis for this rejection in part upon its misunderstanding of the before-discussed counting of peptide deletions as conservative substitutions for the sole purpose of determining the percentage of substitution. A further basis for this rejection rests on the assertion that "[p]rotein chemistry is probably one of the most unpredictable areas of biotechnology" that was followed by several statements and references to published articles that were said to "demonstrate that even a single amino acid substitution or what appears to be an inconsistent chemical modification will often dramatically affect the biological activity and characteristic of a protein." These bases for rejection cannot be agreed with and are respectfully traversed as discussed below.

It is first noted that none of the articles relied-upon or supplied contained disclosures specifically related to the hepatitis B core protein, changes in the sequence of that molecule, and possible changes to the resulting function. Those articles are submitted to be irrelevant to the present claims as the articles teach nothing about the claimed protein whose structure and function are different from each of those proteins discussed in those articles. Inasmuch as there are neither asserted nor perceived similarities in structure or function between any protein of the articles and a chimer protein claimed here, no predictive value relative to the claimed subject matter is seen from the teachings of any of those articles.

It is further noted on this point that the HBc protein itself has little biologic activity in the use disclosed in this application other than as a carrier of an immunogen. As a

consequence, one does not worry here about the nuances of receptor binding for a growth factor or proteolytic degradation or the like that are discussed in the relied-on articles to the extent that one might in other fields of protein biochemistry.

It is submitted that the present application contains more than sufficient enablement to permit a worker of ordinary skill at the time of the filing to make and use the invention claimed to the full breadth of the claims without undue experimentation. It is thus believed and submitted that this basis for rejection should be withdrawn.

C. Rejections Under 35 USC §102(b)

1. Zlotnick et al.

(a) Claims 1, 12-18, 36-38,
51-60, 63-65 and 68-71; and

(b) Claims 51-60

It is understood from the Action that the separate rejections of claims 1, 12-18, 36-38, 51-60, 63-65 and 68-71 and 51-60 as being anticipated by the disclosures of the paper by Zlotnick that was document A29 of the IDS have been withdrawn. That withdrawal is noted with appreciation.

2. Ireland et al.

Claims 1-8, 18, 27-28, 32-33, 42, 63 and 75 were again rejected as allegedly anticipated by the disclosures of Ireland US Patent No. 5,990,085. That patent teaches the insertion of a peptide sequence from the inhibin molecule into the HBC molecule

at one of two positions. The first is at position 144 of a truncated HBc whose C-terminal final HBc residue is at position 144, whereas the other construct places the inhibin peptide within the sequence of full-length core at position 78.

The prior Action argued that an Ireland chimer C-terminally truncated at position 144 having a cysteine at native HBc position 107 "satisfies a limitation" of a claimed chimer because the Cys residue at position 107 was "about 30 residues from the C-terminus of the chimer molecule". That misreading of the claim language was refuted in the prior Reply by providing the entire phrase from the claim in context as shown below.

(b) contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule...

However, the present Action asserted rereading the quoted claim language and still asserted that the interpretation argued in the prior Reply was "one possible interpretation of a claim passage that is far from crystal clear."

Neither the prior nor the present Action explained or asserted what was unclear about the phrase complained of. Instead, both have asserted the unsupported conclusion that a residue about 37 residues toward the N-terminus from the C-terminal residue of the HBc sequence is at a location in the linear sequence that is 180 degrees in the other direction in the linear sequence and that the recited language is broad enough to encompass both. In as much as no explanation was provided in either Action as to how one could construe a residue stated to be "toward the C-terminus" from the "C-terminal residue of the HBc sequence" as being toward the N-terminus of

the HBC sequence, it is requested that such an explanation be provided if this basis for rejection is maintained.

It is again submitted that because the whole basis for this rejection is based on an unexplained and unsupported mischaracterization of the claim language, this basis for rejection should be withdrawn and Ireland should be withdrawn as a reference against the claims.

It is further submitted that the recently decided case of *Phillips v. AWH Corp.* No. 03-1269, -1286, 2005 U.S. App. LEXIS 13954, (Fed. Cir. July 12, 2005) is instructive here. That case dealt primarily with claim construction. After discussing a lessened role of dictionaries in interpreting the claims than had been asserted in some prior cases, Judge Bryson writing for the Court turned to the role of the specification for such interpretation.

Judge Bryson pointed out a distinction between reading the claims in light of the specification and reading limitations into the claims from the specification. The Court maintained that how a person of ordinary skill in the art would understand the claims was the important point. Continuing, Judge Bryson pointed out that the purpose of the specification is to teach and enable those of skill in the art to make and use the invention and to provide the best mode for doing so. He noted that "[o]ne of the best ways to teach a person of ordinary skill in the art how to make and use the invention is to provide an example of how to practice the invention in a particular case." *Phillips v. AWH Corp.* at *54-59.

Following Judge Bryson's advice, the Examiner's attention is invited to the several Examples that begin at page 100 and continue through page 176. It is submitted that in each of those examples, the cysteine residue is at a position carboxy

terminal to the last residue in the HBc sequence and no construct, other than used for comparison to show a lack of stability, relies on the cysteine at residue position 107.

Thus, using the specification as Judge Bryson teaches in *Phillips*, a skilled worker sees make and use, as well as best mode for constructs where the C-terminal Cys is at a location that is C-terminal to the last HBc sequence residue. That skilled worker also sees use of constructs containing the 107 Cys as the most C-terminal cysteine residue as the unstable sequence that is compared to the stabilized sequence. It is submitted that a skilled worker would not understand the unstable comparator to be that which is claimed here where an increase in stability is claimed. It is therefore again submitted that this basis for rejection should be withdrawn.

C. Rejection Under 35 USC §103(a)

(1) Pumpens In View Of Zlotnick

Claims 1-9, 12-33, 35-38, 42-78 were again rejected as allegedly obvious over the disclosures of Pumpens (1995), in view of Zlotnick, noted previously. The prior Action contained a second rejection of claims 1, 2, 9, 12-18, 24, 32, 33, 36-38, 42, 45, 51-60, 63-66, 68-71, 75 and 78 based on those two teachings. The second rejection was not per se repeated, but inasmuch as the same claims were rejected and the prior arguments overlap with the assertions of the present rejection, it is presumed that that rejection has been subsumed into the present single rejection, and both are dealt with here. This rejection is again respectfully traversed.

The present Action dismissed its erroneous prior reliance on the full length chimeras of Pumpens' Table 1 that contain a heterologous epitope by saying that both Pumpens and Zlotnick

teach C-terminally truncated molecules and reasons for their truncation. Of course, Pumpens has no stabilization at the C-terminus of a truncated molecule and Zlotnick has neither an inserted epitope, nor a suggestion of where to put one. In addition, neither relied-on disclosure teaches that a particle formed from C-terminal truncated HBc chimers including an inserted sequence has decreased stability relative to a truncated sequence or a full-length 183-Cys-containing sequence that includes an inserted sequence.

As to the linkers disclosed by Pumpens, those linkers are DNA polylinker sequences. If a rejection is maintained based upon the presence of those relied-on DNA sequences that are portions of DNA polylinker sequences being present within a claimed sequence, it is requested that an explanation also be provided as to how one might manufacture such a material and how such a material would qualify as a "protein" as is recited in claim 1.

The Action next asserts that Zlotnick followed the erroneous statement in Pumpens concerning a stabilizing effect of sequences added internally to C-truncated HBc chimers, but no disclosure is found in Zlotnick concerning any inserted sequence. The combining of the two disclosures is rather the result of a hindsight expedition looking for bits and pieces of unrelated art that could be put together to seem to make up a whole but have no conceptual glue to keep itself together.

The thrust of the Zlotnick disclosure was concerned with the morphology of HBc capsid particles and whether those particles were greater or smaller in size based on the length of the C-terminal region. Those authors found that the "C terminus of the assembly domain (residues 140-149) functions as a morphogenic switch, longer C termini favoring a higher

proportion of the larger capsids, ..." (Abstract.) It is thus submitted that the Action has highlighted a portion of the Zlotnick teaching that was incidental to that disclosure and used there merely as a control study, taken it out of context, combined it with contrary teachings of Pumpens to arrive at the present claims. In making that hindsight reconstruction, the Action still has the disclosure of Pumpens concerning a stabilizing feature of added internal sequences in C-truncated chimeras to dispose of in finding motivation to combine the teachings, and utterly fails to deal with the issue. This basis for rejection should be withdrawn.

(2) Thornton et al. In View Of Zlotnick

Withdrawal of the rejection of claims 61, 62, 76 and 77 as allegedly obvious from the combined teachings of Thornton US Patent No. 5,143,726 in view of Zlotnick as discussed above is noted with appreciation.

D. Provisional Double-Patenting Rejection

Withdrawal of the provisional rejection of claims 1-78 under the judicially created doctrine in view of the recently filed Terminal Disclaimer over claims 1-46 of Serial No. 10/732,862 is noted with appreciation.

E. Further Art

In reviewing the Action and art cited and provided in the information disclosure statements, it was noted that a paper cited in the specification at page 48 [Koschel et al., *J. Virol.*, 73(3):2153-2160 (Mar. 1999)] was inadvertently omitted from the submissions. A copy of that paper is enclosed as

document C1 and the paper is cited on the enclosed Form PTO-1449. A check for the late fee is also enclosed.

F. Summary


Claims 1, 18, 51, 63 and 75 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 
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Enclosures

Exhibits 1 through 4.

Petition for One-Month Extension of Time and fee

Document C1, Form PTO-1449 and fee



CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures, Petition for One-Month Extension of Time and its fee are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on September 8, 2005.

By Edward P. Gamson
Edward P. Gamson

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